Stability Analysis of the Ribosome Flow Model

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Abstract—Gene translation is a central process in all living organisms. Developing a better understanding of this complex process may have ramifications to almost every biomedical discipline. Recently, Reuveni *et al.* proposed a new computational model of this process called the *ribosome flow model* (RFM). In this study, we show that the dynamical behavior of the RFM is relatively simple. There exists a unique equilibrium point e and every trajectory converges to e. Furthermore, convergence in monotone in the sense that the distance to e can never increase. This qualitative behavior is maintained for any feasible set of parameter values, suggesting that the RFM is highly robust. Our analysis is based on a contraction principle and the theory of monotone dynamical systems. These analysis tools may prove useful in studying other properties of the RFM as well as additional intracellular biological processes.

Index Terms—Gene translation, systems biology, computational models, monotone dynamical systems, tridiagonal cooperative systems.

1 Introduction

The protein coding potential inscribed in a species' DNA is converted into proteins through the process of gene expression. The major steps of this process are transcription, translation, and mRNA and protein turnover. Thus, gene translation is a central cellular process, with ramifications related to every biomedical discipline including human health [1], [2], [3], [4], [5], [6], [7], biotechnology [8], [9], [10], [11], [12], evolution [3], [13], [14], [15], [16], [17], [18], [19], functional genomics [20], [21], [22], [23], [24], [25], [26], and systems biology [27], [28], [29], [30], [31], [23], [5]. Recently, several comprehensive reviews related to translation have been published in the leading scientific literature [32], [14], [10].

In the recent years, computational models of translation have been developed and employed to address questions in all the disciplines mentioned above (see, for example, [33], [34], [35], [36], [37], [38]). Mathematical analysis of these computational models is important for several reasons. It can deepen our understanding of the translation process, lead to efficient algorithms for optimizing gene translation, and assist in improving the fidelity of computational models.

In this paper we consider a recent computational model of translation–the *ribosome flow model* (RFM) [39]. We show that the dynamical behavior of the RFM is simple. There exists a unique equilibrium point e and every trajectory converges to e. Furthermore, convergence is monotone, as the distance to e can never increase. This qualitative behavior is maintained for any feasible set of parameter values, suggesting that the RFM is highly robust. Our analysis is based on the theory of monotone dynamical systems [40], [41], [42].

The remainder of this paper is organized as follows. The next subsection describes the RFM derived in [39]. Section 2 presents our main results. Section 3 reviews some known results that will be used later on. The proof of our main result is given in Section 4. The final section concludes and describes some interesting open problems that deserve further research.

1.1 The Ribosome Flow Model

The conventional model of translation elongation is the *Totally Asymmetric Simple Exclusion Process* (TASEP) [36], [35], [43]. The TASEP is a general stochastic model for traffic-like movement, that is, movement that takes place on some kind of tracks or trails. The tracks are modeled by a lattice of sites and the moving objects by particles that can hop, with some probability, from one site to a neighboring one. The term "simple exclusion" refers to the fact that hops may take place only to a target site that is not already occupied by another particle. The motion is assumed to be asymmetric in the sense that there is some preferred direction of motion. The term "totally asymmetric" refers to the case where motion is allowed only in one direction. The TASEP has been used to model and study a large number of biological systems, ranging from extracellular transport to pedestrian dynamics [44].

TASEP models for translation are based on the following assumptions. Initiation time as well as the time a ribosome spends translating each codon are random variables (*e.g.* with an exponential distribution) and are codon dependent. In addition, ribosomes span over several codons and if two ribosomes are adjacent, the trailing one is delayed until the ribosome in front of it has proceeded onwards (see Fig. 1). Despite its rather simple description, it seems that rigorous analysis of the TASEP is non-trivial.

Reuveni *et al.* [39] recently introduced a simpler deterministic model called the *ribosome flow model* (RFM) (see

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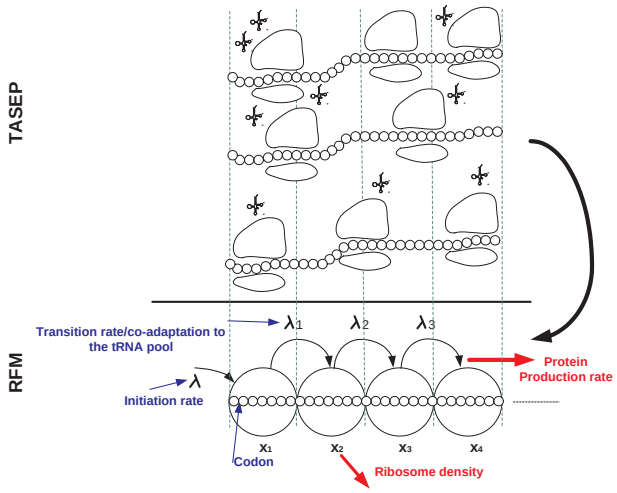

Fig. 1. The TASEP and the RFM. Upper-part: The TASEP model: each codon has an exponentially distributed translation time; ribosomes have volume and can block each other. Lower-part: The RFM is a coarse grained mean field approximation of the TASEP.

Fig. 1). In the RFM, mRNA molecules are coarse-grained into n sites of codons. Ribosomes reach the first site with initiation rate λ, but are only able to bind if this site is not already occupied by another ribosome. In practice, the initiation rate is a function of physical features such as the number of available free ribosomes and nucleotide context surrounding initiation codons [39], [10], [45], [37], [34]. A ribosome that occupies site i moves, with transition rate $\lambda_i > 0$, to the consecutive site provided the latter is not already occupied by another ribosome.

As demonstrated in [39], simulations of the full TASEP and the simpler RFM yield similar predictions of translation rates. For example, the correlation between their predictions of translation rates over the set of endogenous genes of *S. cerevisiae* is 0.96.

Denoting the probability that site i is occupied at time t by $x_i(t)$, it follows that the rate of ribosome flow into/out of the system is given by: $\lambda(1-x_i(t))$ and $\lambda_n x_n(t)$, respectively.

The rate of ribosome flow from site i to site $i+1$ is given by $\lambda_i x_i(t)(1-x_{i+1}(t))$, so the RFM is given by:

$$\begin{aligned}
\dot{x}_1 &= \lambda(1-x_1) - \lambda_1 x_1(1-x_2),\\
\dot{x}_2 &= \lambda_1 x_1(1-x_2) - \lambda_2 x_2(1-x_3),\\
\dot{x}_3 &= \lambda_2 x_2(1-x_3) - \lambda_3 x_3(1-x_4),\\
&\vdots\\
\dot{x}_{n-1} &= \lambda_{n-2} x_{n-2}(1-x_{n-1}) - \lambda_{n-1} x_{n-1}(1-x_n),\\
\dot{x}_n &= \lambda_{n-1} x_{n-1}(1-x_n) - \lambda_n x_n. \qquad (1)
\end{aligned}$$

The transition rates $\lambda, \lambda_1, \ldots, \lambda_n$ are positive numbers. The exact values are determined by the codon composition of each site and the tRNA pool of the organism (see the Methods section in [39]).

The state-variables correspond to occupation probabilities, and so we always consider initial conditions $x(0)$ in the closed unit cube:

$$C = \{x \in \mathbb{R}^n : x_i \in [0,1], i = 1, \ldots, n\}.$$

Suppose that $e = (e_1, \ldots, e_n)'$ is an equilibrium point of the RFM, *i.e.* for $x = e$ the right-hand side of all the equations in (1) is zero, so

$$\begin{aligned}
\lambda(1-e_1) &= \lambda_1 e_1(1-e_2)\\
&= \lambda_2 e_2(1-e_3)\\
&\vdots\\
&= \lambda_{n-1} e_{n-1}(1-e_n)\\
&= \lambda_n e_n. \qquad (2)
\end{aligned}$$

Denoting

$$R = \lambda_n e_n \qquad (3)$$

yields

$$\begin{aligned}
e_n &= R/\lambda_n,\\
e_{n-1} &= R/(\lambda_{n-1}(1-e_n)),\\
&\vdots\\
e_2 &= R/(\lambda_2(1-e_3)),\\
e_1 &= R/(\lambda_1(1-e_2)),
\end{aligned} \qquad (4)$$

and

$$e_1 = 1 - R/\lambda. \qquad (5)$$

Combining (4) and (5) provides a finite continued fraction expression for R:

$$1 - R/\lambda = \cfrac{R/\lambda_1}{1 - \cfrac{R/\lambda_2}{1 - \cfrac{R/\lambda_3}{1 - \cfrac{R/\lambda_4}{1 - \cfrac{R/\lambda_5}{\ddots\, 1 - R/\lambda_n}}}}} \qquad (6)$$

Note that if we assume that $e_i \in [0,1]$ for any i, then (2) implies that

$$R \leq \min\{\lambda, \lambda_1, \ldots, \lambda_n\}. \qquad (7)$$

Reuveni *et al.* [39] used (6) to consider two extreme cases. When the ribosome input flux is low, *i.e.* $\lambda \ll \min\{\lambda_1, \ldots, \lambda_n\}$, Eq. (7) yields $R \ll \lambda_i$ for any i, and (6) implies that $1 - R/\lambda \approx 0$, so $R \approx \lambda$. On the other hand, when $\lambda \gg \max\{\lambda_1, \ldots, \lambda_n\}$ Eq. (7) yields $\lambda \gg R$ so we

may approximate (6) by

$$1 \approx \cfrac{R/\lambda_1}{1-\cfrac{R/\lambda_2}{1-\cfrac{R/\lambda_3}{1-\cfrac{R/\lambda_4}{1-\cfrac{R/\lambda_5}{\ddots\, 1-R/\lambda_n}}}}} \tag{8}$$

A solution of this equation has the form $R = R(\lambda_1, \ldots, \lambda_n)$, *i.e.* R (and, therefore, e) will not depend on λ.

The simulations in [39] indicate that the dynamical behavior of the RFM is simple.

Example 1 Consider the model (1) with $n = 3$, $\lambda = \lambda_1 = 1$, $\lambda_2 = 2$, and $\lambda_3 = 3$, *i.e.*

$$\begin{aligned} \dot{x}_1 &= 1 - x_1 - x_1(1 - x_2), \\ \dot{x}_2 &= x_1(1 - x_2) - 2x_2(1 - x_3), \\ \dot{x}_3 &= 2x_2(1 - x_3) - 3x_3. \end{aligned} \tag{9}$$

In this case, (6) becomes

$$1 - R = \cfrac{R}{1-\cfrac{R/2}{1-R/3}},$$

or

$$7R^2 - 17R + 6 = 0.$$

This equation admits two solutions: $R = 2$, corresponding to $(-1, 3, 2/3)'$ (that is not in C), and $R = 3/7$ corresponding to

$$e = (4/7, 1/4, 1/7)'. \tag{10}$$

Fig. 2 depicts the trajectories of (9) for several initial conditions in C. It may be seen that each trajectory remains in C, and converges to the equilibrium point e. □

The next section details our main results. Let

$$Int(C) = \{x \in \mathbb{R}^n : x_i \in (0, 1),\ i = 1, \ldots, n\},$$

i.e. the interior of C.

2 Main result

Our first result shows that any trajectory of the RFM emanating from C converges to a unique equilibrium point.

Theorem 1 *Consider the RFM* (1) *with* $\lambda, \lambda_i > 0$. *The RFM admits a single equilibrium point* $e \in Int(C)$. *For any initial condition* $x(0) \in C$, $x(t) \in C$ *for any* $t \geq 0$, *and*

$$\lim_{t\to\infty} x(t) = e.$$

From the biophysical point of view, this result means that perturbations in the distribution of ribosomes on a mRNA will not change the asymptotic behavior of the dynamics. It will still converge to the same unique steady state e, that is, to the same distribution of ribosomes and the same translation rates. In particular, a simulation of the RFM from any initial condition will converge to the same final state. This agrees of course with the simulation results reported in [39]. Changing the values of the positive paraments λ, λ_i will not change this qualitative behavior; however, it will change the exact location of e in $Int(C)$, that is, the distributions and the translation rates at the steady state.

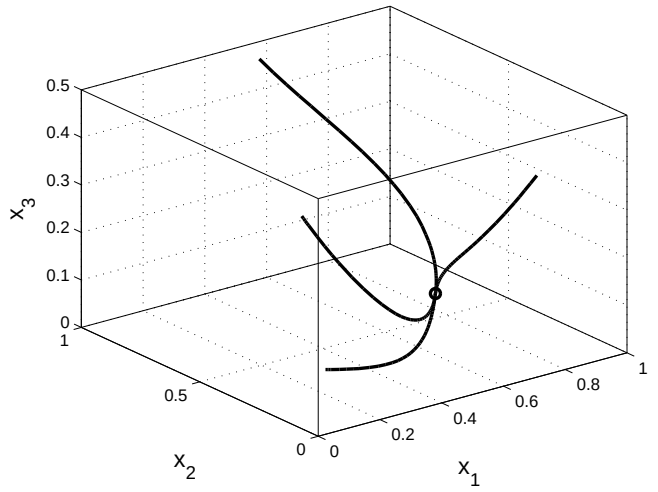

Fig. 2. Trajectories of (9) for four different initial conditions in the unit cube. The equilibrium point e in (10) is marked with a circle.

Theorem 1 does not provide any information on what happens until convergence. Our second result considers the robustness of an entire trajectory of the RFM with respect to perturbations of the initial condition.

Let $x(t; x_0)$ denote the solution of the RFM at time t for the initial condition $x(0) = x_0$. Recall that the L_1 norm of a vector $x \in \mathbb{R}^n$ is $|x|_1 = \sum_{i=1}^n |x_i|$.

Theorem 2 *Fix arbitrary* $a, b \in C$. *Then*

$$|x(t; a) - x(t; b)|_1 \leq |a - b|_1, \tag{11}$$

for any $t \geq 0$.

In other words, the L_1 distance between trajectories is always bounded by the L_1 distance between their initial conditions. In particular, two trajectories that emanate from close initial conditions will remain close for any $t \geq 0$. From the biological point of view, this result suggests that the difference between two ribosomal density profiles can never increase.

Note that taking $b = e$ in (11) yields

$$|x(t; a) - e|_1 \leq |a - e|_1, \quad \text{for all } t \geq 0.$$

In other words, the convergence to e is monotone, as the L_1 distance to e can never increase.

The proof of our results is based on a contraction principle and on the theory of *monotone dynamical systems* (see, *e.g.* the monograph [40]). In particular, we use Smillie's theorem on tridiagonal monotone systems [42]. In the next section, we review some known results that will be used later on.

3 PRELIMINARIES

3.1 Monotone systems

Let $\Omega \subset \mathbb{R}^n$ be an open set. Consider a system of n ordinary differential equations

$$\dot{x} = f(x), \tag{12}$$

where $f : \Omega \to \mathbb{R}^n$ is continuously differentiable. For $t \geq 0$ and $x_0 \in \Omega$, let $x(t; x_0)$ denote the solution of (12) at time t for the initial condition $x(0) = x_0$. For the sake of simplicity, we assume from here on that $x(t; x_0)$ exists for any $t \geq 0$.

For two vectors $a, b \in \mathbb{R}^n$, we write $a \leq b$ if $a_i \leq b_i$ for $i = 1, \ldots, n$. We write $a < b$ if $a \leq b$ and $a_i < b_i$ for some i, and we write $a \ll b$ if $a_i < b_i$ for any i.

Definition 1 The vector field $f : \Omega \to \mathbb{R}^n$ is said to satisfy the *Kamke condition* if for any two vectors $a, b \in \Omega$ satisfying $a \leq b$ and $a_i = b_i$ we have

$$f_i(a) \leq f_i(b).$$

The Kamke condition implies that the flow of (12) is *monotone* in the following sense.

Proposition 1 *[40, Chapter 3] Let $<_r$ denote any of the relations $\leq$, $<$, or $\ll$. Suppose that the vector field f in* (12) *satisfies the Kamke condition. Then for any $x_0 <_r y_0$,*

$$x(t; x_0) <_r x(t; y_0) \text{ for all } t \geq 0.$$

The easiest way to verify that the Kamke condition holds is based on the sign structure of the Jacobian matrix $\frac{\partial f}{\partial x} : \Omega \to \mathbb{R}^{n \times n}$, *i.e.* the matrix whose ij entry is $\frac{\partial f_i}{\partial x_j}$. If Ω is convex and

$$\frac{\partial f_i}{\partial x_j}(x) \geq 0, \text{ for any } i \neq j \text{ and any } x \in \Omega, \tag{13}$$

then the Kamke condition holds. Indeed, by the fundamental theorem of calculus for line integrals (see, e.g., [46]),

$$f_i(b) - f_i(a) = \int_0^1 \sum_{j=1}^n \frac{\partial f_i}{\partial x_j}(a + (b-a)r)(b_j - a_j)dr.$$

If $a_i = b_i$ then this simplifies to

$$f_i(b) - f_i(a) = \int_0^1 \sum_{\substack{j=1 \\ j \neq i}}^n \frac{\partial f_i}{\partial x_j}(a + (b-a)r)(b_j - a_j)dr,$$

and if $a \leq b$ then (13) yields $f_i(b) - f_i(a) \geq 0$.

Intuitively speaking, (13) implies that a positive change in x_j increases $f_i(x)$. Since $\dot{x}_i = f_i(x)$, this implies that different state variables reinforce each other. A system (12) that satisfies (13) is called a *cooperative system*.

If a cooperative system satisfies $\frac{\partial f_i}{\partial x_j} = 0$ for any $|i - j| > 1$, then the system is said to be a *tridiagonal cooperative system* [42]. If, furthermore, $\frac{\partial f_i}{\partial x_j} > 0$ for $|i - j| = 1$, then the system is called a *strongly cooperative tridiagonal system* (SCTS).

Recall that a set in $\mathbb{R}^n$ is called *compact* if it is closed and bounded. The next result shows that the dynamical behavior of any *bounded* trajectory of a SCTS is relatively simple.

Theorem 3 *[42] Let $\dot{x} = f(x)$ be a SCTS defined on an open set $\Omega \subset \mathbb{R}^n$. Assume that the functions f_i are $n-1$ times differentiable. Let $x : [0, a) \to \mathbb{R}^n$ be a solution of the system defined on some maximal interval of time $[0, a)$ with $0 < a \leq \infty$. Then either: (1) $\lim_{t \to a} x(t)$ exists and is an equilibrium point of the dynamics; or (2) as $t \to a$, $x(t)$ eventually leaves any compact set.*

3.2 Contraction principle

We now briefly review a *contraction principle* that will be used in the proof of Theorem 2. For more details, see [47, Chapter 3], [48], [49]. Given a vector norm $|\cdot| : \mathbb{R}^n \to \mathbb{R}_+$, the induced matrix norm $||\cdot|| : \mathbb{R}^{n \times n} \to \mathbb{R}_+$ is

$$||A|| = \max_{|x|=1} |Ax|,$$

and the induced *matrix measure* $\mu : \mathbb{R}^{n \times n} \to \mathbb{R}$ is

$$\mu(A) = \lim_{\epsilon \downarrow 0} \frac{1}{\epsilon}(||I + \epsilon A|| - 1).$$

To gain an intuitive interpretation of $\mu(A)$, consider the linear equation $\dot{y} = Ay$. Then, up to a first-order approximation

$$\begin{aligned} y(t + \epsilon) &= y(t) + \epsilon Ay \\ &= (I + \epsilon A)y(t), \end{aligned}$$

so $|y(t + \epsilon)| \leq ||I + \epsilon A||| y(t)|$, and

$$\frac{1}{\epsilon}(|y(t + \epsilon)| - |y(t)|) \leq \frac{1}{\epsilon}(||I + \epsilon A|| - 1)|y(t)|.$$

Hence,

$$\frac{d^+}{dt}|y(t)| \leq \mu(A)|y(t)|,$$

where d^+/dt denotes the right-hand derivative.

Theorem 4 *(Contraction principle) Consider the equation*

$$\dot{x} = f(x), \tag{14}$$

with f continuously differentiable. Let $J : \mathbb{R}^n \to \mathbb{R}^{n \times n}$ denote the Jacobian of f. Suppose that a convex set $K \subseteq \mathbb{R}^n$ is an invariant set for (14)*, and that there exists a vector norm $|\cdot| : \mathbb{R}^n \to \mathbb{R}$ for which the induced matrix measure satisfies*

$$\mu(J(x)) \leq r,$$

for any $x \in K$. Then for any $a, b \in K$ and any $t \geq 0$,

$$|x(t;a) - x(t;b)| \leq e^{rt}|a - b|.$$

For a self-contained proof of this result, see [48].

4 PROOFS

An immediate yet crucial observation is that the RFM (1) is a SCTS on the open unit cube $Int(C)$. For example, since $\dot{x}_2 = f_2(x)$, with $f_2(x) = \lambda_1 x_1(1-x_2) - \lambda_2 x_2(1-x_3)$, we have $\frac{\partial f_2}{\partial x_i}(x) \neq 0$ only for $i = 1, 2, 3$. Also ,for any $x \in Int(C)$,

$$\frac{\partial f_2}{\partial x_1}(x) = \lambda_1(1 - x_2) > 0,$$

and

$$\frac{\partial f_2}{\partial x_3}(x) = \lambda_2 x_2 > 0.$$

The biological interpretation of this property is simple. First, the chain–like structure of the RFM (see Fig. 1) implies that the dynamics $f_2(x)$ at site 2 can depend only on $\{x_1, x_2, x_3\}$. Second, if more ribosomes occupy site 1, then more ribosomes will proceed to site 2. Also, If more ribosomes occupy site 3, then more ribosomes in site 2 are delayed, so in both cases there exists a positive feedback effect on the change in the concentration of ribosomes in site 2.

Let $\partial C = C \setminus Int(C)$, *i.e.* the boundary of C. To prove Theorem 1 we require the following result.

Proposition 2 *For any $x(0) \in Int(C)$, the solution of* (1) *satisfies $x(t) \in Int(C)$ for any $t \geq 0$.*

In other words, the open unit cube is an *invariant set* of (1).

Proof. Seeking a contradiction, assume that $x(0) \in Int(C)$ yet there exists a (first) time $T > 0$ such that $x(T) \notin Int(C)$. Then $x(T) \in \partial C$, so $x_k(T) \in \{0, 1\}$ for at least one index k. This implies that at least one of the following two cases holds.

Case 1. There exists a (minimal) index i such that

$$x_i(T) = 0, \tag{15}$$

and $x_j(T) > 0$ for any $j < i$. If $i = 1$, Eq. (1) implies that $\dot{x}_1(T) = \lambda > 0$. Since $x_1(t) \in (0, 1)$ for any $t < T$, this implies that $x_1(T) > 0$. We conclude that the case $i = 1$ is not possible, so $i > 1$. Now (1) implies that $\dot{x}_i(T) = \lambda_{i-1} x_{i-1}(T)$. Since $x_j(T) > 0$ for any $j < i$, this implies that $\dot{x}_i(T) > 0$, so $x_i(T) > 0$. This contradicts (15), so we conclude that Case 1 is not possible.

Case 2. There exists a (maximal) index i such that

$$x_i(T) = 1,$$

and $x_j(T) < 1$ for any $j > i$. If $i = n$, Eq. (1) implies that $\dot{x}_n(T) = -\lambda_n < 0$. Since $x_n(t) \in (0, 1)$ for any $t < T$, this implies that $x_n(T) < 1$. We conclude that the case $i = n$ is not possible, so $i < n$. Now (1) implies that $\dot{x}_i(T) = -\lambda_{i+1}(1 - x_{i+1}(T))$. Since $x_j(T) < 1$ for any $j > i$, this implies that $\dot{x}_i(T) < 0$, so $x_i(T) < 1$. We conclude that Case 2 is also not possible. This contradiction implies that $Int(C)$ is an invariant set of the RFM. □

The next result shows that a trajectory emanating from the boundary of the unit cube enters the unit cube.

Proposition 3 *For any $x(0) \in \partial C$ there exists a time $t > 0$ such that $x(t) \in Int(C)$.*

Proof. Assume that $x(0) \in \partial C$, *i.e.* $x_k(0) \in \{0, 1\}$ for at least one index k. Again, this implies at least one of two cases.

Case 1. There exists a (minimal) index i such that $x_i(0) = 0$ and for any $j < i$, $x_j(0) > 0$. We will show that

$$x_i(\tau) \in (0, 1) \text{ for some } \tau > 0. \tag{16}$$

If $i = 1$, then (1) yields $\dot{x}_1(0) = \lambda > 0$, so (16) indeed holds. If $i > 1$, then

$$\dot{x}_i(0) = \lambda_{i-1} x_{i-1}(0),$$

and since $x_{i-1}(0) > 0$, this implies that $\dot{x}_i(0) > 0$ so again (16) holds. Note that it follows from the proof of Proposition 2 that for any $j < i$, $x_j(t) \in (0, 1)$ for any $t \geq 0$. Thus, $x_k(\tau) \in (0, 1)$ for any $k \in \{1, \ldots, i\}$, and then $x_k(t) \in (0, 1)$ for any $k \in \{1, \ldots, i\}$ and any $t \geq \tau$.

Case 2. There exists a (maximal) index i such that $x_i(0) = 1$ and for any $j > i$, $x_j(0) < 1$. A similar argument shows that $x_i(\tau) \in (0, 1)$ for some $\tau > 0$.

Summarizing, the state-variable with minimal index i such that $x_i(0) = 0$ enters C at some time $t > 0$. Inductively, this implies that there exists a time $\eta > 0$ such that $x_i(\eta) > 0$ for any $i \in \{1, \ldots, n\}$. Similarly, there exists a time $\zeta > 0$ such that $x_i(\zeta) < 1$ for any $i \in \{1, \ldots, n\}$ and any $t \geq \zeta$. This completes the proof of Proposition 3. □

We can now prove Theorem 1. Since the RFM is a SCTS and $Int(C)$ is an invariant set, Theorem 3 implies the existence of at least one equilibrium point $e \in Int(C)$. We will show that there exists a *single* equilibrium point in $Int(C)$. Seeking a contradiction, assume that $e, \tilde{e} \in Int(C)$ are two different equilibrium points. Then (4) implies that (6) admits at least two different real solutions R, $\tilde{R}$ corresponding to e and $\tilde{e}$, respectively. Without loss of generality, assume that

$$R < \tilde{R}. \tag{17}$$

The first equation in (4) implies that $e_n < \tilde{e}_n$. Then the second equation implies that $e_{n-1} < \tilde{e}_{n-1}$, and proceeding in this fashion yields $e_1 < \tilde{e}_1$. Combining this with (5) and the fact that $R, \tilde{R} > 0$ (this follows from (3)) yields $R > \tilde{R}$. This contradicts (17). We conclude that there exists a *single* equilibrium point $e \in Int(C)$. Applying Theorem 3 implies that for any $x(0) \in Int(C)$, the trajectory $x(t)$ converges to e. For any $x(0) \in \partial C$, the trajectory goes inside C and then again $x(t)$ converges to e. This completes the proof of Theorem 1. □

We now turn to the proof of Theorem 2. Recall that for the L_1 vector norm $|\cdot|_1$, the induced matrix measure

of a matrix $A \in \mathbb{R}^{n\times n}$ is

$$\mu_1(A) = \max_{1\le j\le n}(A_{jj} + \sum_{\substack{1\le i\le n\\ i\neq j}} |A_{ij}|), \tag{18}$$

i.e. the maximum of the column sums, with non diagonal elements replaced by their absolute values [47, Chapter 3].

Proposition 4 *For the RFM* (1),

$$\mu_1(J(x)) = 0, \quad \textit{for any } x \in C. \tag{19}$$

Proof. It is straightforward to verify that for any $i \neq j$, $J_{ij}(x) \geq 0$ for any $x \in C$. Thus, we can ignore the absolute value in the column sums in (18). The first column of J contains only two non-zero entries, namely, $J_{11} = -\lambda - \lambda_1(1 - x_2)$ and $J_{21} = \lambda_1(1 - x_2)$, so $J_{11} + J_{21} = -\lambda < 0$. Similarly, the sum of elements in the nth column of J is $J_{n-1\,n} + J_{nn} = \lambda_{n-1}x_{n-1} - \lambda_n - \lambda_{n-1}x_{n-1} = -\lambda_n < 0$. For any $1 < i < n$, column i of J contains three non-zero elements: $J_{i-1\,i} = \lambda_{i-1}x_{i-1}$, $J_{ii} = -\lambda_{i-1}x_{i-1} - \lambda_i(1-x_{i+1})$, and $J_{i+1\,i} = \lambda_i(1-x_{i+1})$, so the column sum is zero. □

Combining Theorem 4 with (19) yields (11). This completes the proof of Theorem 2. □.

5 Discussion

Our results show that the RFM has several nice properties. There exists a unique equilibrium point e and any trajectory emanating from a feasible initial condition converges to e. Also, the L_1 distance between two trajectories can never increase.

From the biophysical point of view, this means that perturbations in the distribution of ribosomes on a mRNA will not change the asymptotic behavior of the dynamics. It will still converge to the same distribution of ribosomes and the same translation rates. In particular, a simulation of the RFM from any initial condition will converge to the same final state. This provides a rigorous explanation for the simulation results reported in [39]. Also, the difference between two profiles of ribosome densities is a non-increasing function of time.

Changing the values of the paraments λ, λ_i will not change this qualitative behavior, but it will change the distributions and the translation rates at the steady state.

Our analysis is based on the theory of monotone dynamical systems. These systems proved be to a useful tool for modeling a variety of biochemical networks. Sontag [41] provides several explanations for the applicability of monotone systems in this context: (1) the behavior of monotone systems is ordered and predictable; (2) the quantitative behavior is highly robust with respect to changes in parameter values (this is particulary important in biological networks where exact parameter values are often hard to determine); and (3) it is often useful to model large systems as interconnections of monotone subsystems.

The RFM has been used for describing translation elongation. However, it can be used (with a different set of parameter values and some additional changes) for describing other intracellular processes. One such process is *transcription elongation* [50]. In this process the DNA molecule is transcribed by RNA polymerases to mRNA molecules. More than one RNA polymerase can transcribe the same DNA molecule simultaneity, polymerases have volume, they can block each other, and their local speed is determine by DNA sequence near them. However, in the case of transcription, the RNA polymerases may also move backwards, leaving a newly synthesized 3'-end of nascent RNA hanging out and available for exonucleases [51]. Thus, in order to model the transcription process the RFM should be modified accordingly. Another relevant process is intracellular trafficking of motor proteins along the microtubule or microfilament network. As each microtubule is a relatively long rope-like polymer, all the major features of the translation process also appear here. Thus, the results reported here may be relevant also to these cases.

Several open questions deserve further research. First, the *rate of convergence* to e is of importance. One tool for deriving bounds on the rate of convergence is a *Lyapunov function* (see, *e.g.*, the very readable presentation in [52]). Roughly speaking, a Lyapunov function is a function $V : \mathbb{R}^n \to \mathbb{R}_+$ that satisfies

$$\dot{V}(x(t)) \leq 0$$

along any trajectory of the dynamic system. One may think of V as associating to each state x the "energy" of the system when in state x. If this energy is continuously decreasing then the state must converge to the point corresponding to minimal energy. Fiedler and Gedeon [53] derived an iterative procedure for constructing a Lyapunov function V for a SCTS. The resulting Lyapunov function has the form

$$V(x) = -\sum_{i=1}^{n-1} g_i(x_i, x_{i+1}) - g_n(x_n),$$

and along trajectories of the SCTS,

$$\dot{V}(x(t)) = -\sum_{i=1}^{n} a_i(x(t))(\dot{x}_i(t))^2.$$

The a_is here are positive functions, so $\dot{V}(x(t)) \leq 0$ with equality if and only if $\dot{x}_i(t) = 0$ for any i, that is, if and only if $x(t)$ is an equilibrium point. An interesting feature of V is that it is the sum of "local" functions $g_i(x_i, x_{i+1})$ that take into account the interaction between two consecutive state-variables only. This approach is applicable of course for the RFM. However, it leads to a rather contrived V,[1] and it is not clear yet if this V can be used to derive information on the convergence rate.

1. For example, for the RFM with $n = 2$, $V(x_1, x_2) = g_1(x_1, x_2) + g_2(x_2)$, with $g_1 = \lambda(x_1 - \frac{x_1^2}{2}) - \lambda_1\frac{x_1^2}{2}(1-x_2)$, and $g_2 = -\frac{\lambda_2^2}{2\lambda_1}(2\ln(1-x_2) + x_2 + \frac{1}{1-x_2} - 1)$.

Another interesting question is the sensitivity of e to changes in the RFM parameters λ, λ_i specifically in comparison to the phase transitions in the TASEP [43], [54]. In real biological systems, one usually analyzes thousands of genes in multiple organisms corresponding to different sets of parameter values. Understanding the dependence of the steady state on the parameter values may be used to considerably accelerate the simulations by initiating the trajectory in the vicinity of the steady state.

In addition, it is reasonable to assume that the translation process is controlled by some form of feedback, so the analysis of an extended version of the RFM that includes a suitable feedback loop may be of interest. Note that there are several interesting analytic results on the behavior of monotone systems under a feedback connection (see, *e.g.* [55], [56]).

The RFM, as all mathematical models, provides a trade-off between simplicity and realism. In particular, the RFM is an efficient approximation of the TASEP [43] yet it does not take into account several aspects of the translation process. These include: (1) the existence of multiple initiation sites or programmed frameshifting [57]; (2) the effect of strong RNA secondary structures that may delay ribosomes; and (3) recoding–encoding Selenocysteine in a special way by a UGA codon [58] (see, for example, [59] for additional reading about datasets and a statistical approach to such translation events). The RFM may serve as the basis for developing a more sophisticated and more realistic mathematical model of translation.

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